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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,047	12/21/2001	Brian K. Kaspar	66671-092	5129

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EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,047	KASPAR ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claims 1, 2, 8, 9, 10, 18, and 19 are objected to because of the following informalities: The status of these claims should be --currently amended-- not simply "amended". Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 10-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 10 and dependent claims have been amended to recite that the purpose for the method is "enhancing the survival" of a nerve cell (claim 10). Except for claim 12, the claims do not limit the environment of nerve cell. The nerve cell being treated may be a cultured nerve cell (except for claim 12), or a nerve cell in any animal having nerve cells. Applicant points to para. 0018 as supporting the amendment. It is presumed that by para. "0018," Applicant is referring to the paragraph on page 8 that follows the paragraph labeled "0017," rather than the paragraph

labeled "0018" appearing on page 13. Page 8 refers to therapeutic applications involving administering vectors to mammals, e.g. to enhance survival of neurons specifically in nervous systems. However, claims 10, 11, and 13-18 are not limited to treating neurons *in vivo,* much less neurons in mammals, while claim 12 is not limited to treating neurons in mammals. Consequently, the claims embrace subject matter beyond the scope of the original disclosure, e.g. applying the method to neurons in culture or in non-mammalian animals. There is no evidence of record that applicant had contemplated or was in possession of such embodiments embraced by the amended claims at the time the application was filed. This rejection would be overcome by limiting claim 10 to nerve cells in mammals, with cancellation of claim 12 which would then be a duplicate of claim 10 in terms of its scope.

Claims 19-27 remain rejected and claims 10-18 are rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 10/30/03 because the specification, while being enabling for promoting survival in humans of: a) entorhinal layer II neurons by intrahippocampal injection, or b) nigral-TH positive neurons by intrastriatal injection of a viral vector comprising a gene encoding an anti-apoptotic gene of the Bcl-2 family, or promoting survival of spinal motorneurons by intramuscular injection of a viral vector comprising a gene encoding insulin-like growth factor-1, wherein the genes are expressed, does not reasonably provide enablement for any other embodiments embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 10-18 are directed to a method for enhancing survival of neurons. Although the claims do not explicitly require the method to be practiced *in vivo*, the specification does not describe using the claimed method on neurons *in vitro*, and as indicated above, the alleged support in the original specification for amended claim 10 describes only carrying out the method on neurons in a nervous system, i.e. *in vivo*.

Applicant's arguments filed 4/30/04 have been fully considered but they are not persuasive. Applicant argues that Orkin, Verma, and Rosenberg do not support the rejection because none of the references deal specifically with delivery of a viral vector to the synaptic portion of a nerve cell (neuron), such that the vector undergoes retrograde transport. However, the feature upon which Applicant's arguments are based, i.e. retrograde transport, addresses only one aspect in one area of gene therapy – where to deliver the vector in treatment of neurodegenerative disorders. Orkin Verma, and Rosenberg establish that gene therapy as a whole is highly unpredictable and poorly developed, and that despite tremendous endeavor by people highly skilled in the art, little or no clinical success has been attained. Orkin lists several different aspects of gene therapy that posed, and still pose, barriers to achieving clinical success (see pages 4-5 of the previous Office action). Hsich discloses that gene therapy for neurologic disease poses more difficulties than gene therapy in general, due at least in part to the higher complexity of the nervous system and limited scientific understanding of the pathologic process involved and the consequences of expressing "therapeutic" genes (Hsich, pages 594-595). It has long been recognized in the chemical arts that the unpredictability of a particular art area may alone provide a reasonable doubt as to the accuracy of a broad statement made in support of the enablement of a claim. Ex parte Singh, 17 USPQ2d 1714, 1715 (BPAI 1991), In re Marzocchi,

169 USPQ 367, 369-370 (CCPA 1971). As set forth in In re Fisher, 166 USPQ 18, 24 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Applicant asserts that Hsich describes the successful use of viral vectors and retrograde transport, and that this method "is a promising candidate for further optimization". However, Hsich is simply pointing out that viral vectors that undergo retrograde transport have been used successfully to deliver genes to target cell nuclei, not that they have been used successfully for clinical applications or achieving defined therapeutic endpoints, such as the instant claims require. Also, the "promising candidate for optimization of gene delivery" referred to by Hsich are synthetic vectors, such as naked DNA-liposomes. Hsich (pages 594-595) makes very clear that gene therapy in the central nervous system was still in the exploratory phase at the time the instant invention was made. The issue is not whether the use of viral vectors that undergo retrograde transport may eventually be useful in some therapeutic applications, but whether the specification enables the claimed invention as broadly as it is claimed. Hsich clearly indicates that at the time the invention was made, one of skill in the art was aware only of potential applications of gene therapy for treating neurological disease and the extensive problems that had to be solved, and not aware of the necessary information for successfully treating any of them.

Applicant (pages 11-12) asserts that the instant specification comply with the standards for enablement. Applicant (pages 12-14) also asserts that the general teachings of the specification along with the three specific embodiments deemed to be enabled are sufficient to

enable the broad scope being claimed. However, the grounds of rejection addressed these issues and provided evidence from the pertinent art that raise serious doubt for such assertions. Applicant has provided no evidence to the contrary. "Argument of counsel cannot take the place of evidence lacking in the record." *In re Scarbrough*, 182 USPQ 298, 302 (CCPA 1974).

As pointed out by Orkin for gene therapy in general, and by Hsich for gene therapy for neurological disorders, gene therapy for a particular disease would present its own challenges and that the pathophysiology of each disease would have to be understood. Hsich also pointed out the need to determine the effects of a particular therapeutic gene. Simon and Finiels present evidence demonstrating the unpredictability of the effects of particular therapeutic genes in the nervous system. Consequently, one cannot extrapolate from the specific enabled embodiments to predict what products and procedures would be required to achieve other therapeutic outcomes or treat other diseases. The law under §112, first para. requires that the disclosure in the application shall inform those skilled in the art how to use the invention, not how to find out for themselves how to use it. *In re Gardner*, 166 USPQ 138, 141 (CCPA 1970). The specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Tossing out the germ of an idea does not constitute an enabling disclosure. While every aspect of a generic claim need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the skilled artisan to understand and carry out the invention. It is true that a specification need not disclose what is well known in the art. However, that general, oft-repeated statement is

merely a rule of supplementation, not a substitute for a basic enabling disclosure. The rule that a specification need not disclose that which is well known in the art simply means that omission of minor details does not cause a specification to fail the enablement requirement, and is not a substitute for an enabling disclosure. However, if there is no disclosure of starting materials and of conditions under which the process can be carried out, undue experimentation is required. Failure to provide such teachings cannot be rectified by asserting that the disclosure of the missing necessary information was well known in the prior art. See *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 101, 1005 (CA FC, 1997). The specification is silent with regard to guidance critical to carrying out the invention as broadly as it is claimed, such as identifying target neurons, administration sites, and therapeutic genes for treating the range of neurodegenerative diseases. In this case, the prior art is of little or no help at all since those in the art had been unsuccessful in achieving any unequivocal instance of effective treatment with gene therapy in humans. Consequently, due to the high unpredictability in the relevant art and the lack of specific guidance and working examples for the breadth of embodiments embraced by the claims, undue experimentation would be required to carry out the invention as broadly as it is claimed.

Claims 12 and 17 remain rejected under 35 U.S.C. 112, second paragraph, for the reasons of record set forth in the Office action of 10/30/03 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments filed 4/30/04 have been fully considered but they are not persuasive. With respect to claim 12, Exhibits A and B show definitions for the verb "incubate"

and the noun incubation. Applicant concludes from these definitions that those skilled in the art would understand the meaning of "incubate" in the context of the claims. However, it is unclear how sitting upon eggs or maintaining eggs, embryos or bacteria (Exh. A) relates to the context of the invention. Incubation, as it relates to a period of time during an infection process by a pathogen, is a noun, not a verb; there is no corresponding definition for incubate; and it is unclear how it would relate to the context of the invention.

With respect to claim 17, Applicant's arguments and the amendment of claim 18 do not address the rejection, nor has applicant indicated what the term is intended to mean. Original claim 18 is part of the original disclosure, and the only other mention of "nerve growth factor" is at page 22, para. 0047, line 2. It is unclear whether "nerve growth factor", as recited in claim 17, is being used as a generic term embracing all nerve growth (or neurotrophic) factors, as in original claim 18, or apparently NGF specifically, as on page 22. If claim 17 is to embrace NGF specifically, then deleting "a" from "a nerve growth factor" would clarify the issue.

Claim Rejections - 35 USC § 102

Claims 10-12 and 16 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Peterson et al. (European Journal of Neuroscience 12 (Suppl. 11): 233, Abstract 110.13, June 2000) for the reasons of record set forth in the Office action of 10/30/03 as applied to claims 1-4, 8 and 9.

Amended claims 10, 12-15 and 17 are now directed to a method for enhancing survival of neurons. The claims are not limited to human neurons and Applicant's argument in response to the rejection of claimed 1-4, 8 and 9 does not apply to this new rejection.

Claims 1, 2, 4-7, 19, 20, 22-25 remain rejected and claims 10, 12-15, and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Horellou et al., US 2002/0031493 A1 for the reasons of record set forth in the Office action of 10/30/03.

Amended claims 10, 12-15 and 17 are now directed to a method for enhancing survival of neurons. As indicated above, the scope of "nerve growth factor (claim 17) is unclear. If generic, it would embrace GDNF. See Horellou at para. 0006, which describes GDNF as a neurotrophic factor that promotes survival of dopaminergic neurons.

Claims 1, 2, 4-7, 19, 20, 22-24 remain rejected and claims 10, 12-15, and 17 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Finiels et al., US 6,632,427 B1 for the reasons of record set forth in the Office action of 10/30/03.

Amended claims 10, 12-15 and 17 are now directed to a method for enhancing survival of neurons. As indicated above, the scope of "nerve growth factor (claim 17) is unclear. If generic, it would embrace NT-3 (a member of the neurotrophin family, which also includes NGF).

Applicant's arguments filed 4/30/04 have been fully considered but they are not persuasive. Applicant asserts that Horellou and Finiels do not teach transfection of human neurons. However, Horellou (e.g. para. 48 and claim 29) and Finiels (col. 1-2; col. 13, lines 8-41) are directed in part to the treatment of human neurological diseases, such as Parkinson's disease and ALS, which would mean that humans are to be treated and human neurons are to be transfected. In addition, claims 10, 12-15, and 17 are not limited to human neurons.

Claim Rejections - 35 USC § 103

Claims 19-21 and 25-27 remain rejected and claims 1-4, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson et al. (European Journal of Neuroscience 12 (Suppl. 11): 233, Abstract 110.13, June 2000) for the reasons of record set forth in the Office action of 10/30/03.

Applicant's arguments filed 4/30/04 have been fully considered but they are not persuasive. Applicant argues that Peterson does not teach treatment of humans, and that the report in Peterson that the vector and/or protein underwent retrograde transport raises uncertainties. In response, rejection is not made under 35 USC 102, and it is what Peterson would suggest to one of skill in the art with respect to treatment of human Alzheimer's disease that is at issue. One carries out experiments in animal models to determine whether treatment of humans would be efficacious, and the results in Peterson with a rat model of Alzheimer's disease provide a reasonable expectation of success in treating human Alzheimer's disease. That Peterson did not distinguish between retrograde transport of the vector vs. the protein (or both) simply indicates that the authors did not carry out an experiment to clarify this point. However since the procedure disclosed by Peterson is essentially the same as being claimed, the result must also be the same.

Double Patenting

Claims 1-9 and 19-27 remain and claims 10-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over

claims 1-26 of copending Application No. 10/237,567 for the reasons of record set forth in the Office action of 10/30/03.

The subject matter of claims 20-22 when viewed with claims 12-19 of the '567 application is embraced by instant claims 10-16.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicant has not presented arguments in regard to this provisional rejection.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy J. Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

Scott D. Priebe
Primary Examiner
Art Unit 1632